# PHASE 3 SUMMARY OF MRID 00094013:

# 90-DAY TOXICITY STUDY IN RATS

## STUDY # 22102

## FLUMETRALIN

GUIDELINE REFERENCE:

82-1(A) 90-DAY FEEDING - RODENT

SUMMARY PREPARED BY:

JACQUELINE GILLIS, Ph.D.

MERRILL TISDEL

14 SEPTEMBER 1990

ORIGINAL STUDY PREPARED BY:

LITTON BIONETICS, INC.

KENSINGTON, MARYLAND

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

Company: CIBA-GEIGY Corporation (Typed Name)

Company Agent: Thomas Parshley (Typed Name)

Title: Senior Reg. Specialist

Signature: _____ Date: _____

These data are the property of the Agricultural Division of CIBA-GEIGY Corporation, and as such, are considered to be confidential for all purposes other than compliance with FIFRA §10. Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any other statute or in any other country.

HAZLETON
LABORATORIES AMERICA, INC.

LBI 22102-01

COMPLIANCE STATEMENT
Three Month Oral Toxicity Study in Rats
CGA-41065 Technical

This study was conducted in compliance with the Good Laboratory Practice Regulations as set forth in Title 21 of the U.S. Code of Federal Regulations Part 58, issued December 22, 1978 (effective June 20, 1979), and with any applicable amendments. Findings from the inspections and final report review were reported to management and to the study director.

Study Director:

for N. NICKI HAMADA, Ph.D., D.A.B.T.
Life Sciences Division

9/28/90
Date

GOOD LABORATORY PRACTICE STATEMENT

This study does not meet the requirements for 40 CFR part 160 (see above)

Submitter/Sponsor of Study

Merrill Tisdel
Agricultural Division
CIBA-GEIGY Corporation
Greensboro, North Carolina

PM3006899726

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Certification of Availability of Raw Data

I hereby certify that the submitter possesses or has access to the raw data used in or generated by the study summarized in this document.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

Certification of Accuracy of Summary and Adequacy of the Study

I certify, in compliance with FIFRA section 4(e)(1)(A), that this summary accurately represents the data presented in the report(s) of this study cited by MRID, and that this study fully satisfies all pertinent requirements of the OPP Guideline it addresses.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

R406MT0628MG

## 82-1 Subchronic Feeding in the Rodent and Nonrodent

### ACCEPTANCE CRITERIA

**Does your study meet the following acceptance criteria?**

1. Y Technical form of the active ingredient tested.
2. Y At least 10 rodents or 4 nonrodents/sex/group (3 test groups and control group).
3. Y Dosing duration daily for 90-days or 5 days/week for 13 weeks.
4. Y Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit dose if nontoxic (1000 mg/kg).
5. Y Doses tested include a NOEL.
6. * Y Analysis for test material stability, homogeneity and concentration in dosing medium
7. Y Individual daily observations.
8. Y Individual body weights.
9. Y Individual or cage food consumption.
10. * Y Opthalmoscopic examination (at least pretest and at term) control and high dose.
11. Y Clinical pathology data of 12 & 13 at termination for rodents; for nonrodents at the beginning then either monthly or midway and at termination.
12. Y Hematology.
    - Y Erythrocyte count
    - Y Hemoglobin
    - Y Hematocrit
    - Y Leucocyte count
    - * Y Differential count
    - Y Platelet count (or clotting measure)
13. Y Clinical chemistry.
    - * Y Alkaline phosphatase
    - Y Aspartate aminotransferase
    - * N Creatinine kinase
    - Y Alanine aminotransferase
    - * Y Lactic dehydrogenase
    - Y Glucose
    - Y Bilirubin
    - * Y Cholesterol
    - * Y Creatinine
    - Y Total Protein
    - Y Albumin
    - Y Urea nitrogen
    - N Inorganic phosphate
    - Y Calcium
    - * Y Potassium
    - Y Sodium
    - * Y Chloride
14. * Y Urinalysis, only when indicated by expected or observed activity. As scheduled in 11.
    - Y Blood
    - Y Protein
    - Y Ketone bodies
    - Y Appearance
    - Y Glucose
    - Y Total bilirubin
    - * Y Urobilirubin
    - Y Sediment
    - Y Specific gravity (osmolality)
    - * N Volume
15. Y Individual necropsy of all animals.

Criteria marked with a * are supplemental and may not be required for every study.

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16. Y/N Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

| | | |
|---|---|---|
| Y aorta | Y jejunum | Y peripheral nerve |
| Y eyes | Y bone marrow | Y kidneys† |
| Y caecum | Y liver† | Y esophagus |
| Y colon | Y lung | Y ovaries |
| Y duodenum | Y lymph nodes | N oviduct |
| Y brain† | Y stomach | Y pancreas |
| Y skin | Y mammary gland | N rectum |
| Y heart | Y spleen | Y spinal cord (3x) |
| Y testes† | Y musculature | Y thyroid / parathyroids |
| Y pituitary | N epididymis | Y salivary glands |
| Y ileum | Y adrenals | Y thymus |
| Y trachea | Y urinary bladder | |
| NA gall bladder | Y accessory sex organs; uterus | |

† organs to be weighed

Criteria marked with a * are supplemental and may not be required for every study.

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## IDENTIFICATION OF TEST MATERIAL

### Chemical Name

CAS Name: N-(2-Chloro-6-fluorobenzyl)-N-ethyl-α,α,α,-trifluoro-2,6-dinitro-p-toluidine

or

2-Chloro-N-[2,6-dinitro-4-(trifluoromethyl)phenyl]-N-ethyl-6-fluorobenzenemethanamine

Common Name: Flumetralin

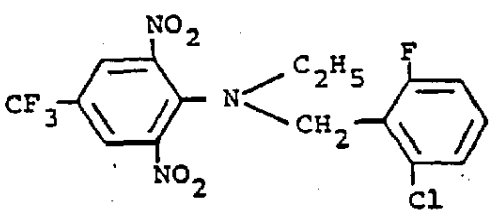
Trade Name: Prime +®

CIBA-GEIGY Code Number: CGA-41065

CAS Registry Number: 62924-70-3

EPA Shaughnessy Number: Unknown

Chemical Structure:




### Percent Active Ingredient

92% minimum

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Flumetralin: 82-1(A): Subchronic Feeding in the Rodent

1. The test article was Flumetralin (CGA-41065) Technical, a bright orange crystalline substance, FL-810772, purity 92.7%.

2. There were 20 male and 20 female albino rats (CRL:COBS CD(SD)BR) in four primary study groups (control and three dose levels). An additional five male and five female rats in the control and high-dose groups served as recovery animals, i.e., they were treated with the primary groups for 13 weeks, then switched to the basal diet only and sacrificed after an additional four weeks. Also, ten additional male and female rats were sacrificed prior to dosing for pre-dose control clinical pathology determinations.

3. Animals in the three primary test groups were administered the test article in feed daily for a total of 13 weeks. Animals in the control group were fed the basal diet mixed with the vehicle (acetone) for 13 weeks. Animals in the recovery groups were fed the basal diet only for an additional four weeks.

4. The doses tested were 30 ppm, 300 ppm, and 1500 ppm. Six animals died while on study, but none of the deaths were perceived to be related to treatment. Observations for possible pharmacological and/or toxicological effects did not reveal any treatment-related findings in any of the treated groups. Body weights of high-dose males and females were consistently lower than controls throughout the study, but there were no differences among the groups in food consumption. Ophthalmoscopic examinations were unremarkable. At Week 13, hemoglobin was lower in mid- and high-dose males and high-dose females than controls, and hematocrit was lower in high-dose females than controls, but these differences were not found after the recovery period. Levels of BUN and cholesterol were elevated in high-dose males and cholesterol was elevated in high-dose females at Week 13; these differences were not apparent after the recovery period. For high-dose females, spleen weight, spleen/body weight ratio, and spleen/brain weight ratio were significantly higher than controls in the main study group but not in the recovery group. The only treatment-related gross necropsy finding was yellow discoloration of body fat in nearly all high-dose male and female animals. No consistent gross lesions were considered to be treatment-related. The only histopathologic lesion which appeared to be treatment-related was hyaline droplet degeneration in the kidneys of high-dose males. However, this lesion was not found in recovery group animals.

5. The no-observable-effect level for all of the parameters assessed in the study was 30 ppm.

6. Test article concentration in the diets was assessed at Weeks 1, 5, 9, and 13. Analytical concentrations were within ±5% of target concentrations for the three dietary doses. Homogeneity was assessed for the 30 and 1500 ppm diets at Week 1; diet samples averaged 99.1 and 99.9% of target concentrations for the 30 and 1500 ppm diets, respectively. Stability of the test article in feed was determined to be at least seven weeks under refrigeration.

7. All animals were observed daily for mortality and signs of pharmacological and/or toxicological effects. No treatment-related changes were observed. The most common clinical signs were ear tag infection, local hair loss, crust around eyes or inflammation on eyelids, and urine stain on coat. The observation of urine stain on coat was noted almost exclusively in high-dose animals; the orange color of the test article may have made the urine of these animals more visible than that of the lower dose groups.

8. Individual body weights were recorded weekly. For high-dose males and females, mean body weights were consistently lower than controls throughout the study; these differences were statistically significant for males at Weeks 10, 11, 12, and 13, and for females at Weeks 1 and 3. Through 13 study weeks, body weight gain for high-dose animals was approximately 87% and 90% of controls for males and females, respectively.

9. Food consumption data were recorded weekly. Although statistically significant differences were occasionally found among the groups, no consistent patterns were evident for either males or females.

10. Ophthalmoscopic examinations were performed prior to dosing and at the conclusion of the treatment period. No treatment-related findings were observed.

11. Hematology, clinical chemistry, and urinalysis data were collected on all animals prior to the initiation of dosing and at Weeks 6 and 13, and recovery animals only at Week 17. See Items 12, 13, and 14 for results.

12. Hematology measures were hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte counts, platelet count, reticulocyte count, and prothrombin time. Treatment-related differences in erythroid parameters included slightly decreased hemoglobin in mid- and high-dose males and high-dose females at Week 13, and slightly decreased hematocrit in high-dose females at Weeks 6 and 13. There were a few sporadic statistically significant differences in platelet and reticulocyte counts which were inconsistent and not considered to be of toxicologic importance. No differences were found between controls and high-dose males and females after the recovery period.

13. Clinical chemistry measures were sodium, calcium, potassium, lactic dehydrogenase, alanine aminotransferase, aspartate aminotransferase, glucose, urea nitrogen, total, direct, and indirect bilirubin, alkaline phosphatase, total cholesterol, albumin, globulin, a/g ratio, total protein, chloride, uric acid, and creatinine. Statistically significant differences were noted in high-dose animals only. At Week 6, high-dose males showed elevated levels of BUN, cholesterol, potassium, globulin, and total protein, and depressed levels of LDH and alkaline phosphatase; high-dose females showed elevated levels of cholesterol. At Week 13, levels of BUN and cholesterol were elevated in high-dose males and levels of cholesterol were elevated in high-dose females; these differences were not apparent after the recovery period.

14. Urinalysis measures were specific gravity, pH, protein, glucose, ketones, occult blood, bilirubin, urobilinogen, color, appearance, and microscopic examination of formed elements. No differences were apparent between test groups and controls for any of the parameters at any time interval.

15. Animals which survived until study termination were sacrificed at the scheduled terminal sacrifice by $CO_2$ asphyxiation. A gross necropsy examination was performed on sacrificed animals and the six animals which died during the course of the study. Weights were obtained for liver, kidneys, spleen, heart, testes/ovaries, brain, and adrenal glands. Tissue portions of brain (forebrain, midbrain, hindbrain), optic nerve, eyes, Harderian glands, pituitary gland, submaxillary salivary gland, heart, thymus, thyroid gland, parathyroids, lungs with mainstem bronchi, trachea, spleen, cervical and mesenteric lymph nodes, cervical spinal cord, mammary gland, esophagus, stomach, small intestine (duodenum, ileum, jejunum), large intestine (colon, cecum), adrenal glands, pancreas, liver, kidneys, urinary bladder, ovaries/testes, prostate, uterus (corpus, cervix), skeletal

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muscle (thigh), bone with marrow (sternum), descending thoracic aorta, sciatic nerve, and skin. The tissues were fixed in 10% buffered formalin, embedded in paraffin, sectioned at 6 µm, and stained with hematoxylin and eosin.

For males in the high-dose group, terminal body weights were significantly lower than controls and consequently several relative organ/body weight ratios were increased, i.e., liver and spleen for the main study group at 13 weeks and liver, kidney, and brain for the recovery group at 17 weeks. For high-dose females, spleen weight, spleen/body weight ratio, and spleen/brain weight ratio were significantly higher than controls in the main study group but not in the recovery group. Also, terminal body weights for high-dose females were somewhat lower than controls, which contributed to increased liver/body and heart/body weight ratios for the main study groups.

The only treatment-related gross necropsy finding was yellow discoloration of body fat in nearly all high-dose male and female animals.

16. Histopathologic examinations were performed on all preserved tissues of all animals which died on study and all control and high-dose animals. For animals in the low- and mid-dose groups, only liver, kidney, and heart tissues and all gross lesions were examined. Other tissues were not examined because there were no consistent gross lesions that were considered to be treatment-related. The only histopathologic lesion which appeared to be treatment-related was hyaline droplet degeneration in the kidneys of high-dose males. The lesion consisted of accumulations of brightly eosinophilic homogeneous globules in the cytoplasm of proximal tubular epithelial cells. However, this lesion was not found in recovery group animals.

17. There were no significant changes from the Acceptance Criteria in this study. Three deviations from the Acceptance Criteria are noted. Under Item 13, two clinical chemistry parameters, creatinine kinase and inorganic phosphate, were not assessed. Under Item 14, urine volume was not assessed. Under Item 16, lung tissue of low- and mid-dose animals was not examined histopathologically and epididymis, oviduct, and rectum were not examined in any animals. These deviations are considered to be insignificant because none of the study data indicated that additional data from these parameters would have aided in identifying target organs or effect levels.

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